Importance and outcome relevance of central pathology review in prostatectomy specimens: data from the SAKK 09/10 randomized trial on prostate cancer

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Abstract: OBJECTIVES: To conduct a central pathology review within a randomized clinical trial on salvage radiation therapy (RT) in the presence of biochemical recurrence after prostatectomy to assess whether this results in shifts of histopathological prognostic factors such as the Gleason Score. PATIENTS AND METHODS: A total of 350 patients were randomized and specimens of 279 (80%) of the patients were centrally reviewed by a dedicated genitourinary pathologist. The Gleason Score, tumor classification and resection margin status were reassessed and compared with the local pathology reports. Agreement was assessed using contingency tables and Cohen's Kappa. Additionally, the association between other histopathological features (e.g. largest diameter of carcinoma) with rapid biochemical progression (up to 6 months after salvage RT) was investigated. RESULTS: There was good concordance between central pathology review and local pathologists for seminal vesicle invasion [pT3b: 91%; k=0.95 (95% CI 0.89, 1.00)], for extraprostatic extension [pT3a/b: 94%; k=0.82 (95% CI 0.75, 0.89)], and for positive surgical margin status [87%; k=0.7 (95% CI 0.62, 0.79)]. Agreement was lower for Gleason score [78%; k=0.61 (95% CI 0.52, 0.70)]. The median largest diameter of carcinoma was 16 mm (range, 3-38 mm). A total of 49 patients (18%) experienced rapid biochemical progression after salvage RT. Largest diameter of carcinoma [odds ratio (OR): 2.04 (95% Confidence interval (CI): 1.30, 3.20); p = 0.002], resection margin status [OR: 0.36 (95% CI: 0.18, 0.72); p = 0.004] and Gleason score [OR: 1.55 (95% CI: 1.00, 2.42); p = 0.05] remained associated with rapid progression after salvage RT after backward selection. CONCLUSION: The results of the central pathology analyses reveal concordant results for seminal vesicle invasion, extraprostatic extension, positive surgical margin but lower agreement for Gleason Score. Largest diameter of carcinoma was found to be a potential prognostic factor for rapid biochemical progression after salvage RT.

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Importance and outcome relevance of central pathology review in prostatectomy specimens: data from the SAKK 09/10 randomized trial on prostate cancer.

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Running title: Importance of central pathology review

ABSTRACT

Objectives: To conduct a central pathology review within a randomized clinical trial on salvage radiation therapy (RT) in the presence of biochemical recurrence after prostatectomy to assess whether this results in shifts of histopathological prognostic factors such as the Gleason Score.

Patients and Methods: A total of 350 patients were randomized and specimens of 279 (80%) of the patients were centrally reviewed by a dedicated genitourinary pathologist.
The Gleason Score, tumor classification and resection margin status were reassessed and compared with the local pathology reports. Agreement was assessed using contingency tables and Cohen's Kappa. Additionally, the association between other histopathological features (e.g. largest diameter of carcinoma) with rapid biochemical progression (up to 6 months after salvage RT) was investigated.
Results: There was good concordance between central pathology review and local pathologists for seminal vesicle invasion [pT3b: 91%; k=0.95 (95% CI 0.89, 1.00)], for extraprostatic extension [pT3a/b: 94%; k=0.82 (95% CI 0.75, 0.89)], and for positive surgical margin status [87%; k=0.7 (95% CI 0.62, 0.79)]. Agreement was lower for Gleason score [78%; k=0.61 (95% CI 0.52, 0.70)]. The median largest diameter of carcinoma was 16 mm

(range, 3–38 mm). A total of 49 patients (18%) experienced rapid biochemical progression after salvage RT. Largest diameter of carcinoma [odds ratio (OR): 2.04 (95% Confidence interval (CI): 1.30, 3.20); p = 0.002], resection margin status [OR: 0.36 (95% CI: 0.18, 0.72); p = 0.004] and Gleason score [OR: 1.55 (95% CI: 1.00, 2.42); p = 0.05] remained associated with rapid progression after salvage RT after backward selection.

Conclusion: The results of the central pathology analyses reveal concordant results for seminal vesicle invasion, extraprostatic extension, positive surgical margin but lower agreement for Gleason Score. Largest diameter of carcinoma was found to be a potential prognostic factor for rapid biochemical progression after salvage RT.

INTRODUCTION

Patients with biochemical recurrence after prostatectomy without evidence of distant metastatic disease commonly undergo early salvage radiation therapy (RT) of the prostate bed as their major curative treatment approach. There are several established pathological features such as the Gleason Score, tumor classification and resection margin status which can serve as prognostic factors for the outcome after salvage RT and thus must be assessed in a standardized fashion (1, 2). However, it has been previously described that these factors could significantly vary when being assessed by dedicated genitourinary pathologist in a central pathology review (3, 4, 5). This may influence the outcome analyses of clinical trials and therefore the use of central pathology reviews is recommended (6).

Moreover, once centrally reviewed, additional histopathological features can uniformly be assessed which can potentially serve as additional prognostic factors.

It has been described that around one fifth of patients experience rapid biochemical progression after RT and these patients may harbor micrometastatic or radioresistant disease and may require a more tailored treatment approach (7). Thus it it appears to be important to search for clinical and histopathological predictors for rapid biochemical progression.

We describe here the differences between the central and local pathology results for patients treated within our clinical trial on salvage RT and analyze the association of several histopathological features and rapid biochemical progression after salvage RT.

PATIENTS AND METHODS

Trial design and conduct

Between 02/2011 and 04/2014, 350 patients were enrolled in an international phase III randomized controlled trial (Swiss Group for Clinical Cancer Research, SAKK 09/10) on dose-intensified (70 Gy over 7 weeks) versus standard-dose (64 Gy over 6.4 weeks) salvage RT in biochemically relapsed prostate cancer patients without macroscopic disease as previously described (8). The trial was conducted in 28 hospitals (Switzerland: 14, Germany: 11, Belgium: 3). Patients were eligible if they had evidence of biochemical recurrence (two consecutive rises in prostate-specific antigen (PSA) with final PSA >0.1 ng/ml, or 3 consecutive rises) and a PSA at randomization of ≤2 ng/ml. The trial was registered under ClinicalTrials.gov identifier NCT01272050. The full list of inclusion and exclusion criteria can be found at ClinicalTrials.gov web site.

Radical prostatectomy was performed at least 12 weeks before randomization and was not part of this trial. All prostatectomy techniques were permitted. Within 16 weeks prior to randomization, either a MRI (recommended) or a multislice CT of the abdomen and pelvis was mandatory to exclude macroscopic local recurrence or lymph node metastases.

The primary endpoint of the trial was freedom from biochemical progression. The trial was designed as a two-arm phase III trial, assuming a median freedom from biochemical progression ≤ 3.8 years for the null hypothesis, and ≥ 5.8 years for the alternative hypothesis (i.e. absolute difference = 2 years, hazard ratio = 0.6526). The one-sided type I error was 5% and the power 80%. The number of events required for primary analysis was 139, and the sample size 350 patients.

Central pathology Review

The pathological review was performed by a single pathologist with experience in urogenital pathology (VG) and included the examination of all slides of the radical prostatectomy specimen.

Central pathology review was defined as mandatory in the trial protocol. Before centers were opened for accrual a pathology agreement form had to be signed by the main local pathologists stating that its institution is willing to submit slides of the prostatectomy specimen to the central pathology review which was conducted at the department of pathology of the University of Bern, Switzerland. Local pathologists were required to send in hematoxylin-eosin (HE) stained slides pseudonymized together with a report of the local pathology assessment. Gleason Score, tumor classification, presence of extraprostatic

extension, invasion of seminal vesicles, and surgery margin status were recorded. If extracapsular extension was present, its extent was assessed according to Wheeler criteria (focal: neoplastic glands outside the prostate <1 high power field, hpf on ≤2 separat sections neoplastic glands outside the prostate, established: anything more extensive than focal) and sidedness were recorded (anterior, apical, base, posterolateral) (9). Extraprostatic extension was defined as involvement off fat and/or loos connective tissue in plane of fat or beyond, involvement of perienural space in large neurovascular bundles, bulging tumor beyond the normal contours of the prostate gland, sometimes with desmoplastic stromal reaction (9). Positive surgical margin (PSM) status was recorded in case of the presence of tumor cells within the inked margin. For PSM, apical and non-apical (designated as anterior, base, posterolateral or seminal vesicles) involvement was distinguished.

The following local pathology features were obtained by case report form assessment and thus available in the database: tumor classification, Gleason pattern and Score, PSM status.

Central pathology review was carried out according to defined standards (3) and the Gleason Score was assigned according to the 2005 International Society of Urological Pathology (ISUP) consensus (10). Additionally, a new grading system was used to re-classify patients and to compare changes between local and central pathology assessment (11). For tumor classification the 2009 American Joint Committee on Cancer Staging System was used.

Furthermore, the presence of lymphovascular and perineural invasion was assessed, as well as the localization of the largest lesion, the Gleason score within the largest lesion and the largest diameter of carcinoma. These variables were not available for the local pathology assessments and could thus not be compared.

A total of 279 (80% of the 350 trial participants) of prostatectomy specimens provided by local pathologists of 23 centers were reviewed. The remaining samples could not be analyzed because they were not provided by the local pathologists despite multiple reminders.

Statistical analysis

All patients who completed at least one salvage RT session and whose prostatectomy specimens were reviewed by the central pathologist were included in this analysis.

The assessments from local and review pathology were compared using contingency tables and Cohen's Kappa.

PSA doubling time after prostatectomy was calculated from the natural log of 2 divided by the slope of the relationship between the time of PSA measurement and the log of PSA using

linear regression for each patient using all PSA measurements from prostatectomy until randomization.

The PSA values during the first 6 months after completion of salvage RT were used to assess PSA change. Patients were discriminated between rising PSA at any time during the first 6 months after completion of salvage RT (defined as rapid biochemical progression) and PSA response or stable PSA during the first 6 months after completion of salvage RT. Histopathological features were compared between the two patient groups using Wilcoxon rank sum tests for continuous variables and Fisher's exact tests for categorical variables. Furthermore, univariable and multiple logistic regression models with backward selection were applied to investigate the influence of preselected histopathological features and clinical parameters on rapid biochemical progression. Before applying the models pairwise correlations between the variables were investigated descriptively to avoid multicollinearity.

Two-tailed tests with significance level 0.05 were used for all analyses. As no adjustment for multiple testing for these analyses was made, they were exploratory and hypothesis generating. All analyses were performed using SAS 9.4 (SAS Institute) and R 3.2.4 (http://www.r-project.org).

RESULTS

227 (81%) of patients experienced a PSA reduction (n=225) or stable PSA values (n=2) in their first two follow-up visits (3 and 6 months after completion of RT) as compared to the pre-salvage RT value. The remaining 49 patients (18%) experienced rising PSA and were considered as having rapid biochemical progression. Three patients (1%) had missing PSA values after RT.

The median PSA prior to salvage RT was 0.3 ng/mL (range, 0.0 – 1.4 ng/mL) and the median PSA doubling time prior to salvage RT was 7.6 months (range -155.3 – 95.6) and the PSA velocity prior to salvage RT was 0.1 ng/mL/year (range -0.0 – 2.6).

Level of agreement between review and local pathology

There was good concordance between central review and local pathologists regarding seminal vesicle invasion [pT3b: 91%; k = 0.95 (95% CI 0.89, 1.00)], PSM status [87%; k = 0.7 (95% CI 0.62, 0.79)], and for extraprostatic extension [pT3a/b: 94%; k = 0.82 (95% CI 0.75, 0.89)].

Among the 115 patients with extraprostatic extension according to local pathology 108 (94%) were confirmed by central pathology. Of the 164 patients being considered pT2 according to local pathology 146 (89%) were confirmed as pT2 but 18 (11%) were identified to be pT3 according to central pathology review. Thus the proportion of patients with pT3 increased from 41 to 45% after the central pathology review (Table 1).

Of the 152 patients with negative surgical margins according to local pathology, 124 (82%) were confirmed as R0 and 26 (17%) were considered as PSM after central pathology review. For three patients surgical margin status was not available from the central review. Of the 127 patients with PSM according to local pathology, 111 (87%) were confirmed as PSM but 15 (12%) were considered R0. As a result the rate of patients being considered as PSM increased to 49% (pathologic review: 137 of 279 specimens) compared with 45% (local pathologists: 127 of 279).

Agreement was lower for Gleason score (78%; k=0.61 (95% CI 0.52, 0.70)), whereby the pathology review resulted in a shift of the score from lower as well as higher levels to Gleason 7 (Table 2). Interestingly, the agreement was higher for the primary Gleason pattern (k=0.61) than for the secondary Gleason pattern k=0.41) (Table 2). When comparing the new grading system, a similar agreement between local pathology and central review was found (65%; k=0.65 (95% CI 0.58, 0.71)) (data not shown).

Assessment of additional histopathological features

A total of 244 patients (88%) were found to be positive for perineural invasion and a total of 33 patients (12%) were positive for lymphovascular invasion. The median largest diameter of carcinoma was 16 mm (range, 3 – 38 mm). Continuous additional histopathological variables were summarized in Table 3.

Association between clinical and histopathological features and rapid biochemical progression

The results of the comparison of histopathological features between patients with rapid biochemical progression and patients with stable PSA or PSA response are shown in Table 4. After applying multivariable logistic regression models with backward selection, largest diameter of carcinoma [odds ratio (OR): 2.04 (95% Confidence interval (CI): 1.30, 3.20); p = 0.002], resection margin status [OR: 0.36 (95% CI: 0.18, 0.72); p = 0.004] and Gleason score [OR: 1.55 (95% CI: 1.00, 2.42); p = 0.05] remained significantly associated with rapid biochemical progression after salvage RT. In a next step these three variables as well as clinical variables were included in multiple logistic regression models. Again largest diameter, resection margin status and Gleason score remained significantly associated with rapid biochemical progression after salvage RT after backward selection (Table 5).

DISCUSSION

The results of the present central pathology review analysis confirmed a good concordance for major histopathological prognostic factors such as seminal vesicle invasion, extraprostatic extension, positive surgery margin but lower agreement for Gleason Score. Additionally, we could identify the diameter of largest carcinoma as a potential prognostic factor for rapid biochemical progression after salvage RT.

Van der Kwast described the results of a central pathology review of 552 radical prostatectomy specimens. They found a high concordance rate for seminal vesicle invasion (94%, κ=0.83) but the agreement was much less for extraprostatic extension (57.5%, κ=0.33) and for surgical margin status (69.4%, κ=0.45) (3).

Bottke et al. found similar results with a good concordance for seminal vesicle invasion (91%; k = 0.76), and the agreement for extraprostatic extension (75%; k = 0.74) and surgical margin status (84%; k = 0.65) being lower. Again, concordance was much less for Gleason score (47%; k = 0.42) (5).

In an analysis of 2015 radical prostatectomy specimen others have also described a good concordance for seminal vesicle invasion (97.6%; k = 0.82), and the agreement for extraprostatic extension (82.5%; k = 0.59) and surgical margin status (87.5%; k = 0.73) being lower and Gleason Score being less concordant with 54.8% (4).

The concordance rates of our study for seminal vesicle invasion, extraprostatic extension and for PSM status and Gleason score compared well with the results of the three other mentioned studies (3-5).

The difference between the local and central review regarding Gleason score is not surprising. The application of the Gleason grading system changed repeatedly over time and particularly the consensus report by the ISUP 2005 (10), which was used for central pathology review, resulted in a distinct shift of Gleason grades. Since the prostatectomy specimens included in the present study date from different years back to 1998, the differences in Gleason grading can be well explained by these changes in grading practice. Regarding resection margins and extraprostatic extension there is missing standardization and variability between different institutions. This issue was addressed and changed only in the ISUP working group reports on handling and staging of radical prostatectomy specimens (9).

However, the central pathology review relevantly shifted the assessment of important prognostic factors and should therefore routinely be conducted within multicenter clinical trials.

Specifically, the higher total rate of patients being considered as pT3 (45% instead of 41%) and as having a PSM (49% instead of 45%) after central pathology review would have led to more patients undergoing adjuvant RT after radical prostatectomy. On the other hand the shifts recognized by the central pathology review may influence the patients prognosis after RT as provided by a contemporary validated nomogram and are thus of interest (12).

Beyond these standard histopathological features as mentioned above there weren't other histopathological features which were routinely assessed and thus in today´s clinical practice no other pathological variables are being considered as major prognostic factors (2).

We took advantage of the possibility to uniformly assess several other histopathological features which could potentially serve as future prognostic factors. We then divided the patients in men with PSA response or stable PSA and men with rapid biochemical progression in the early phase of follow-up after salvage RT and identified the largest diameter of carcinoma to be independently associated with rising PSA after salvage RT. Patients with rapid biochemical progression likely harbor micrometastatic disease or radioresistant disease and may benefit from more tailored treatment e.g. addition of androgen deprivation therapy (ADT) (7). The prognostic significance of largest diameter of carcinoma has been described controversially, some have described it as independent prognostic factor (13) others as less important (14). Once our trial will have mature biochemical control results we will repeat the analysis to identify prognostic factors and might be able to include some of the histopathological features in a Nomogram (2). No relevant differences in largest diameter of carcinoma were observed between the two treatment arms. Others have described genomic classifier to be able to predict metastases among men receiving salvage RT for biochemically recurrent prostate cancer (15). A combination of histopathological features as assessed by our central pathology review might also be able in helping to detect patients who may benefit from tailored salvage RT treatment in terms of RT dose and / or additional ADT.

This analysis has limitations. Even though central pathology review should have been done in all patients, due to logistical reasons it was only performed in 80% of patients. As patients underwent radical prostatectomy prior to trial enrollment, the prostatectomy specimen were processed according to the standards of the local sites. While the determination of rapid biochemical progression was based on the first regular follow-up visits, biochemical control data has not matured yet and more solid oncological endpoints such as metastasis-free survival are not yet available for analysis.

Conclusion: The results of the central pathology analyses revealed discordant results for seminal vesicle invasion, extraprostatic extension, positive surgical margin as well as

Gleason score. Largest diameter of carcinoma was found to be a potential prognostic factor for rapid biochemical progression after salvage RT.

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CONFLICT OF INTERST DISCLOSURE

There is no conflict of interest to disclose.

Table 1: Distribution of tumor classification after local vs. central pathological assessment

	Pathological tumor classification (local)					**exact concordance**	**under staging by LR vs CR**	**over staging by LR vs CR**
Variable	**pT2a (N=13) n**	**pT2b (N=11) n**	**pT2c (N=140) n**	**pT3a (N=81) n**	**pT3b (N=34) n**	**%**	**%**	**%**
Pathological tumor classification (central)								
. pT2a	9	2	0	0	0	81.8%	0.0%	18.2%
. pT2b	0	2	0	0	0	100.0%	0.0%	0.0%
. pT2c	1	5	127	7	0	90.7%	4.3%	5.0%
. pT3a	3	2	13	74	3	77.9%	18.9%	3.2%
. pT3b	0	0	0	0	31	100.0%	0.0%	0.0%

Table 2: Distribution of primary and secondary Gleason Pattern and Gleason Score after local vs. central pathological assessment

	Primary Gleason pattern (local)					exact concordance	under grading by LR vs CR	over grading by LR vs CR
Variable	**1 (N=1) n**	**2 (N=2) n**	**3 (N=153) n**	**4 (N=114) n**	**5 (N=9) n**	**%**	**%**	**%**
Primary Gleason pattern (central)								
. 3	1	2	128	23	2	82.1%	1.9%	16.0%
. 4	0	0	25	88	2	76.5%	21.7%	1.7%
. 5	0	0	0	3	5	62.5%	37.5%	0.0%
	Secondary Gleason pattern (local)					exact concordance	under grading by LR vs CR	over grading by LR vs CR
Variable	**1 (N=1) n**	**2 (N=3) n**	**3 (N=105) n**	**4 (N=144) n**	**5 (N=26) n**	**%**	**%**	**%**
Secondary Gleason pattern (central)								
. 3	1	2	71	43	6	57.7%	2.4%	39.8%
. 4	0	1	32	99	8	70.7%	23.6%	5.7%
. 5	0	0	2	2	12	75.0%	25.0%	0.0%
	Gleason score (local)							
						exact concordance	under grading by LR vs CR	over grading by LR vs CR
Variable	**2 (N=1) n**	**5 (N=4) n**	**6 (N=31) n**	**7 (N=185) n**	**8 (N=32) n**	**9 (N=26) n**	**%**	**%**	**%**
Gleason score (central)									
. 6	1	1	20	11	1	0	58.8%	5.9%	35.3%
. 7	0	3	11	170	18	5	82.1%	6.8%	11.1%
. 8	0	0	0	3	11	4	61.1%	16.7%	22.2%
. 9	0	0	0	1	2	17	85.0%	15.0%	0.0%

Table 3: Continuous variables of the central pathology review

Variable	Overall (N=279)		
	n	median	(min, max)
Gleason score (central)	279	7.0	(6.0, 9.0)
Largest diameter of carcinoma (mm)	279	16.0	(3.0, 38.0)
Gleason score of largest cancer lesion	279	7.0	(5.0, 10.0)
Diameter of highest Gleason lesion (mm)	279	15.0	(2.0, 38.0)
Percentage of tumor tissue	279	9.0	(0.5, 66.0)
Size of positive resection margin (mm)	133	2.0	(0.3, 90.0)
Gleason score within positive resection margin	132	7.0	(6.0, 10.0)

Table 4: Variables from central pathology review by dichotomized PSA change

	PSA response or stable PSA	Rapid biochemical progression	p-value
Categorical variables			**Fisher's exact test**
Pathological tumor classification (central)			0.5
. pT2a	10 (90.9%)	1 (9.1%)	
. pT2b	2 (100.0%)	0 (0.0%)	
. pT2c	116 (84.1%)	22 (15.9%)	
. pT3a	72 (76.6%)	22 (23.4%)	
. pT3b	27 (87.1%)	4 (12.9%)	
Perineural invasion			0.009
. No	34 (97.1%)	1 (2.9%)	
. Yes	193 (80.1%)	48 (19.9%)	
Seminal vesical infiltration			0.6
. No	199 (81.6%)	45 (18.4%)	
. Yes	27 (87.1%)	4 (12.9%)	
Lymphovascular invasion			0.3
. No	203 (83.2%)	41 (16.8%)	
. Yes	24 (75.0%)	8 (25.0%)	
Extraprostatic growth			0.3
. No	128 (84.8%)	23 (15.1%)	
. Yes	99 (79.2%)	26 (21.0%)	
Resection margins			0.03
. R0	67 (80.7%)	16 (19.3%)	
. R1	69 (93.2%)	5 (6.8%)	
Continuous variables			**Wilcoxon rank sum test**
Gleason score (central)	7.0 (6.0-9.0)	7.0 (6.0-9.0)	0.04
Gleason score of largest cancer lesion	7.0 (5.0-10.0)	7.0 (6.0-9.0)	0.02
Largest diameter of carcinoma (mm)	16.0 (3.0-38.0)	18.0 (9.0-35.0)	0.003
Diameter of highest Gleason lesion (mm)	14.0 (2.0-38.0)	17.0 (2.0-35.0)	0.007
Percentage of tumor tissue	9.0 (0.5-66.0)	13.0 (1.0-51.0)	0.02
Size of positive resection margin (mm)	3.0 (0.3-90.0)	1.0 (1.0-20.0)	0.5

Table 5: Multivariable regression model for the association of variables of the central pathology review and other potentially prognostic variables with dichotomized PSA change

Variable	Odds Ratio (95% CI)	p-value (Wald Chi-Square test)
Results of multiple logistic regression (full model)		
Resection margins (R1 vs R0)	1.64 (1.01-2.65)	0.046
Largest diameter of carcinoma (mm)*	0.32 (0.15-0.69)	0.004
Age at random assignment (years)	1.91 (1.18-3.09)	0.008
BMI (kg/m^2)	1.01 (0.95-1.07)	0.7
Lymphadenectomy performed (no [cN0] vs yes [pN0])	1.01 (0.93-1.10)	0.8
Prostatectomy technique (laparoscopic vs robotically assisted)	0.97 (0.32-2.94)	1.0
Prostatectomy technique (other vs robotically assisted)	2.30 (0.65-8.07)	0.2
Nerve-sparing technique (bilateral vs unilateral)	1.39 (0.53-3.67)	0.5
Nerve-sparing technique (none vs unilateral)	0.73 (0.27-1.97)	0.5
PSA at randomization (ng/mL)	0.85 (0.35-2.11)	0.7
PSA doubling time from prostatectomy to randomization (months)	0.88 (0.25-3.08)	0.8
Results of multiple logistic regression (after backward selection with significance level 0.05)		
Gleason score	1.55 (1.00-2.42)	0.05
Resection margins (R1 vs R0)	0.36 (0.18-0.72)	0.004
Largest diameter of carcinoma (mm)*	2.04 (1.30-3.20)	0.002

Abbreviations: *IQR-normalized for easier interpretation